Glomerular Epithelial Cell Function and Pathology Following Extreme Ablation of Renal Mass

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The role of the pathologic features and dysfunction of glomerular epithelial cells (GECs) in the pathogenesis of glomerular scarring was studied in the remnant kidney model (RK) (1 and 5/6 nephrectomy) in rats. Three weeks after surgery serum creatinine was greater in the RK than either sham-operation controls (SHAM) or spontaneously hypertensive rats (SHRs). Blood pressure was higher in the RK (181 ± 26 mm Hg) than in SHAM (129 ± 17, $P < 0.05$) but not SHR (195 ± 15, $P < 0.05$). GEC endocytosis, assessed by protamine heparin aggregate (PHA) disappearance (10), was not different from that in SHAM. Glomerular damage was greater in RK (glomerular damage index, 30 ± 18) than in SHAM animals (4 ± 3, $P < 0.05$) and SHR (0, $P < 0.05$), and 2 of 11 RK animals had fibrinoid necrosis and thrombosis of arterioles and glomeruli. Segmental sclerosis occurred in only 1 RK animal (0.6% of glomeruli). Six weeks after surgery serum creatinine and urinary protein excretion remained higher in the RK than in the SHAM animals. Blood pressure was higher in RK (158 ± 34 mm Hg) than in SHAM animals (144 ± 24), but the difference was not significant. PHA disappeared from the glomerulus at a slower rate in RK than in SHAM animals (outside the 95% confidence limits of SHAM). Glomerular pathology was more widespread in RK than in SHAM animals (glomerular damage index, 73 ± 62 versus 3 ± 8, $P < 0.05$), and 4 of 11 animals had acute hypertensive injury in arterioles and glomeruli. Segmental glomerular sclerosis was only seen in the animals with necrotic glomeruli. GEC dysfunction is not demonstrable until long after proteinuria and hypertension are established, and it only occurs in the context of severe, acute glomerular injury when the epithelial cells separate from the capillary wall and undergo severe degenerative changes and necrosis. The acute glomerular and vascular lesions in the RK model are morphologically similar to malignant nephrosclerosis in humans. Segmental glomerular sclerosis occurs only after proteinuria is well established in the context of severe glomerular injury, and it appears to represent, at least partially, progression of more proximate glomerular capillary injury. (Am J Pathol 1987, 126:315–324)

PROTEINURIA develops in the rat soon after uninephrectomy and infarction of approximately two-thirds of the remaining kidney.[1-6] The proteinuria is of glomerular origin and has been ascribed to both size and charge-selective defects in the glomerular capillary wall.[4] The association between proteinuria and progressive glomerular scarring that develops has suggested that the remnant kidney is a model for both focal glomerular sclerosis in humans with the nephrotic syndrome and chronic renal disease of diverse causes in which marked reduction in functioning renal mass is associated with progressive glomerular sclerosis and proteinuria.[1,2,4,5,7] The glomerular pathologic features of the remnant kidney have been described in detail by several investigators, and a number of features suggest that the glomerular epithelial cell (GEC) is involved early in the evolution of this lesion. The changes that have been described include hypertrophy and swelling of the cells,[5] increased pinocytosis,[2] the presence of membrane-bound, protein-filled cytoplasmic droplets,[2,4,8] and focal foot process "fusion".[2,8] As the disease progresses, further GEC changes described are vacuolization, "blebs," and focal separation from the basal lamina.[2,4,8] This latter feature allows direct communication between the denuded basal lamina and the urinary space. In the late phase the GECs undergo degeneration and ne-

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crosis,[5] and there is destruction and scarring of the capillary wall.[7,9]

We studied glomerular pathologic features and GEC endocytic function by the method of protamine–heparin aggregate (PHA) disappearance[10] in the rat remnant kidney to determine whether there was evidence for early injury to this cell which could lead to disruption of the integrity of the glomerular capillary wall and capillary tuft scarring. In addition, serial histologic observations were made for determination of the nature of the pathologic features associated with, and therefore probably underlying the sclerosis that occurs in the glomerulus.

Materials and Methods

Animals

Male Sprague–Dawley (SD) rats, weighing 200–250 g, were purchased from Biolab, Chicago, Illinois, and fed water and Prolab R-M-H 3000 (Agway, Inc., Syracuse, NY) (24% protein) *ad libitum*. Spontaneously hypertensive rats (SHRs) were studied in order to provide control observations on glomerular pathology at hypertensive levels of systemic arterial pressure. SHRs, weighing 200–250 g, were purchased from Harlan Laboratories (Indianapolis, Indiana) and followed until their systolic blood pressure exceeded the range seen in the animals with remnant kidneys (150–180 mm Hg).

Renal Ablation and Sham Operation Controls

The rats were anesthetized with sodium pentobarbital (45 mg/kg) given via the tail vein and supplemented as needed. They were placed on an operating table maintained at body temperature. The abdomen was opened through a midline incision; and after ligation of the renal artery, the right kidney was removed. The hilus of the left kidney was visualized, and all but one of the extrarenal branches of the left renal artery were ligated. This resulted in the infarction of from two-thirds to five-sixths of the kidney. The abdomen was closed in layers, and the animal was allowed to recover. The sham operation controls had a laparotomy, and both renal hila were visualized and manipulated, but no arteries were ligated. The SHRs did not undergo sham operations.

Partial ablation of the left kidney by arterial ligation resulted in variable amounts of viable remnant parenchyma. In animals with only three extrarenal branches of the renal artery we ligated two vessels, infarcting two-thirds. When one of the major branches divided before entering the kidney, we ligated all but one of the secondary branches, infarcting five-sixths of the kidney. We did not separately analyze the 1 and ⅚ and 1 and ⅔ abated animals. Variability in the vascular anatomy was a potential source of postoperative mortality. Of 33 ablated animals, 3 died within 1 week, and the remnant kidney was totally infarcted. Three additional animals operated upon died between 1 and 3 weeks, and 2 died 3–6 weeks after ablation. Results are given only for the surviving animals.

Blood Pressure Measurements

Blood pressure was measured with an occlusive tail cuff (model B60 type sensing cuff, amplified by a IITC model 59 amplifier from IITC Life Sciences (Woodland Hills, Calif), and recorded with a Bausch and Lomb Omniscribe Recorder (Houston Instruments, Austin, Tex). This procedure was performed in a warm, quiet room on unanesthetized animals. Although training resulted in reproducible blood pressures in most rats, some animals became agitated, and the measurements, which were obtained with difficulty, may not have been reliable.

Serum Creatinine

Serum creatinine was determined with an autoanalyzer (Creatine Analyzer 2, Beckman, Instruments, Palo Alto, Calif).

Protein Excretion

Urine collections were obtained for 24-hour intervals in metabolic cages. Proteinuria was assessed by the quantitative sulfosalicylic acid method with human serum albumin serving as the standard.

Morphologic Studies

Tissue from the remnant kidney, sham operation control SD rats, and SHRs was processed for light and electron microscopy. After removing small samples for electron microscopy, a transverse section through the papilla of the kidney was fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were cut at 4 μ and stained with hematoxylin and eosin (H & E), periodic acid–Schiff (PAS), Masson's trichrome, and phosphotungstic acid hematoxylin. For electron microscopy the tissue was fixed in 2% glutaraldehyde, 2% paraformaldehyde in 100 mM sodium cacodylate buffer, ph 7.4, to which 10 mM $CaCl_2$ was added.[11] The tissue was cut into 1-mm cubes in a drop of fixative and fixed 4–6 hours in the cold. It was postfixed in OsO_4 in the same buffer for 1

hour and embedded in Medcast by standard techniques. Ultrathin sections of glomeruli were stained with uranyl acetate and lead citrate and viewed and photographed in a Philips EM 301.

Protamine Heparin Aggregate Disappearance

Protamine heparin aggregates (PHAs) were introduced into the lamina rara externa of the glomerular basal lamina (LRE) by the intravenous injection of protamine sulfate (Eli Lilly Company, Indianapolis, Ind), 3 mg/100 g body weight, followed 60 seconds later by heparin (beef lung sodium heparin, The Upjohn Company, Kalamzoo, Mich), 300 units/100 g body weight. Sequential renal biopsies were performed with rats under ether anesthesia, at 5, 30, 60, 90, 120, and 180 minutes after the injection. The biopsies were shallow cortical specimens, measuring approximately 2 mm in greatest dimension, and Gelfoam was used to obtain hemostasis at the biopsy site. Tissue for electron microscopy was fixed and processed as above. The numeric density of the PHA in the LRE at each point was determined with the use of a morphometric technique that we have reported in detail.[10] Three glomeruli from each biopsy were sectioned, and 8 fields from each glomerulus were photographed in a Philips 301 electron microscope. Foci in which GECs were disrupted or separated from the basal lamina were excluded from the analysis. The results were expressed as the number of PHA/100 μ of glomerular basal lamina. We plotted the numeric density at each time interval, expressed as the percentage of the numeric density at 5 minutes, against time on a semilogarithmic scale to obtain disappearance curves.

Statistical Analysis

Blood pressure, renal function, and glomerular damage were compared between groups with the Student unpaired *t* test with Bonferroni's probabilities for multiple comparisons. Linearity of the disappearance curves was determined by calculating the regression coefficient for each animal. The significance of the regression coefficient for the different groups was determined by the Student *t* test. Half-disappearance times were calculated using regression analysis and compared by the Student *t* test. The 95% confidence limits of the regression statistic were calculated by a standard statistical method.[12]

Semiquantitative Histologic Studies

The overall glomerular injury index was calculated by a modification of the technique of Olson et al.[13] One hundred glomeruli were sequentially evaluated. A numeric score was assigned to each glomerulus as a function of its histologic abnormality: O, normal; I, mild glomerular abnormalities, including swelling and hypertrophy of GECs, PAS-positive GEC droplets, and mesangial hypercellularity; 2, segmental glomerular abnormalities, including scarring, hyalinosis, mesangial sclerosis, and necrosis; 3, glomerular necrosis, including destruction of capillary walls, thrombosis, karyorrhexis macrophage infiltration, and fibrinoid necrosis. We multiplied numeric score by 100 to obtain the injury index. In addition, relative involvement of superficial cortical and juxtamedullary nephrons was assessed by separately evaluating 20 of the deepest glomeruli and comparing involvement with that in 20 consecutive glomeruli in the superficial two rows adjacent to the renal capsule. The arteries and arterioles in the kidney were examined for the presense of fibrinoid necrosis and thrombosis.

Experimental Design

Three groups of animals were studied: the remnant kidney model, sham operation controls, and SHRs. Baseline data obtained before surgery and before sacrifice at 3 or 6 weeks after surgery included body weight, blood-pressure, serum creatinine, and 24-hour urinary protein excretion. In 6 rats with remnant kidneys and 4 sham operation controls followed for 6 weeks, interim blood pressure and renal function studies were obtained after 3 weeks, and these data are included in Table 1. Histologic studies were performed on the remnant kidney model and the sham operation controls three and six weeks after surgery. The SHRs were studied by light microscopy only after 3 weeks. PHA disappearance studies were performed on 4 rats with remnant kidneys and 4 sham operation controls 3 weeks after surgery and on 3 remnant kidney rats and 3 controls after 6 weeks. These animals were prospectively designated for these studies.

Results

Blood Pressure and Renal Function

The ablated (Table 1) animals continued to grow, and their body weights were not different from the sham operation controls at 3 (298 $\pm$ 45 versus 300 $\pm$ 36 g, mean $\pm$ SD) and 6 weeks (356 $\pm$ 58 versus 359 $\pm$ 42 g) or from the SHRs at 3 weeks (307 $\pm$ 35 g). When the remnant kidney animals were compared with the sham operation controls, serum creatinine, urinary protein excretion, and blood pressure were significantly elevated by 3 weeks, and the serum creat-

Table 1—Blood Pressure and Renal Function*

	Serum creatinine (mg/dl)	Urinary protein excretion (mg/24 hr)	Blood pressure (mm Hg)
Baseline			
Remnant kidney (23)	0.6 ± .1	8 ± 3†	120 ± 13†
Sham (14)	0.6 ± .1	8 ± 2	120 ± 28
SHR (9)	0.6 ± .1	16 ± 5	199 ± 12
Three weeks			
Remnant kidney (17)§	1.2 ± .4†‡	37 ± 28‡	177 ± 40‡
Sham (8)‖	0.6 ± .1	11 ± 5	129 ± 17
SHR (9)	0.6 ± .1	15 ± 3	195 ± 15
Six weeks			
Remnant kidney (12)	1.4 ± .5‡	55.2 ± 75.2‡	150 ± 50
Sham (10)	0.7 ± .3	12 ± 10	144 ± 24

*Results are given as mean ± SD. Numbers in parentheses indicate the number of animals in which observations were made.
†The mean is significantly different from the SHR value.
‡The mean is significantly different from the sham operation control value.
§Includes interim values of 6 remnant kidney rats followed for 6 weeks.
‖Includes interim values of 4 sham operation controls followed for 6 weeks.

inine and albumin excretion were greater than the sham operation control at 6 weeks. Blood pressure in the remnant kidney animals remained elevated over the shams at 6 weeks, but the difference was not significant. The rise in blood pressure observed in the sham operation controls may have resulted from damage sustained during surgery, but since the three sham operation rats with blood pressures ≥ 160 mm Hg had normal serum creatinine, protein excretion, and renal morphologic characteristics, it is more likely that these elevated blood pressures were acute physiologic events. Before surgery the SHRs had higher blood pressure and greater protein excretion than the remnant kidney animals, whereas the serum creatinine measurements were similar. After three weeks, the remnant kidney animals' blood pressure had risen to the same level as the SHRs', and the serum creatinine and protein excretion became greater than the SHRs'.

Morphologic Studies

Three Weeks After Ablation

The most widespread light-microscopic glomerular changes were swelling and vacuolization of the GECs, which contained many PAS-positive droplets (Figure 1). By electron microscopy the GECs contained electron-dense lysosomes (Figure 2). Although there was focal foot process fusion, the GECs appeared well preserved, and there was no separation of the GECs from the basal lamina. In 2 animals segmental necrosis involved approximately 5% of the glomeruli. Although most of the blood vessels were unremarkable, 2 animals with florid glomerular lesions had thrombosis of arterioles (Figure 3) and fibrinoid necrosis, which occasionally extended into the glomerulus (Figure 4). The pathologic changes are reflected in the overall glomerular damage index (Table 2), which demonstrated significantly more disease in the ablated animals than in the sham operation controls and the SHRs. There was no difference in the distribution of the lesions between juxtamedullary and cortical glomeruli. Only 1 animal showed segmental sclerosis (0.6% of the glomeruli); and although 6 animals had hyalinized glomeruli, they involved less than 1% of the total in every instance. The ischemic areas, adjacent to infarcted cortex, contained many small, shrunken glomeruli and were not included in the analysis.

Six Weeks After Ablation

The pathologic changes seen after 6 weeks of ablation were similar to those after 3 weeks, but they were more widely distributed. Swelling and vacuolization

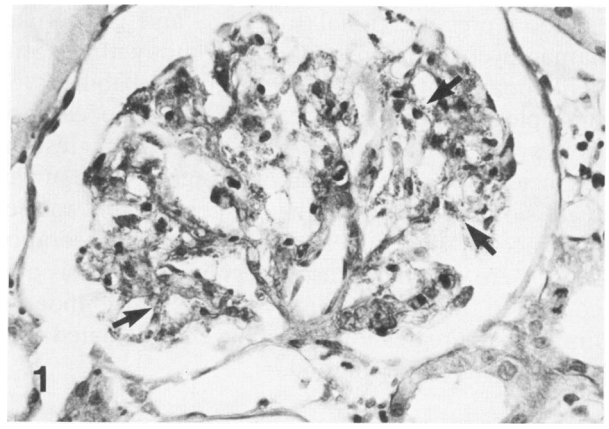


Figure 1—Glomerulus from remnant kidney 3 weeks after ablation. The epithelial cell cytoplasm contains PAS-positive droplets seen in this picture as fine granules in the cytoplasm (*arrows*). The glomerulus shows some shrinkage, but there is no necrosis or scarring. (PAS, ×260)

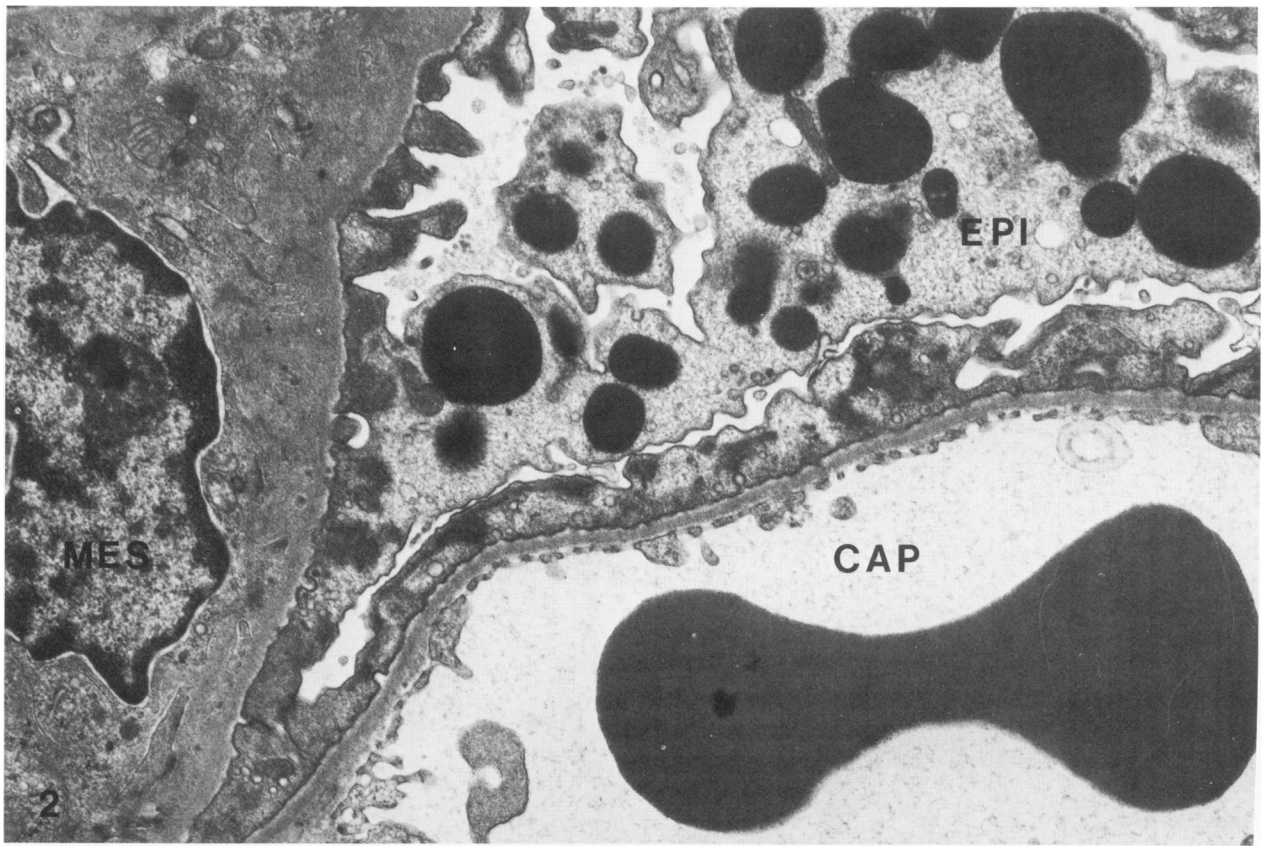
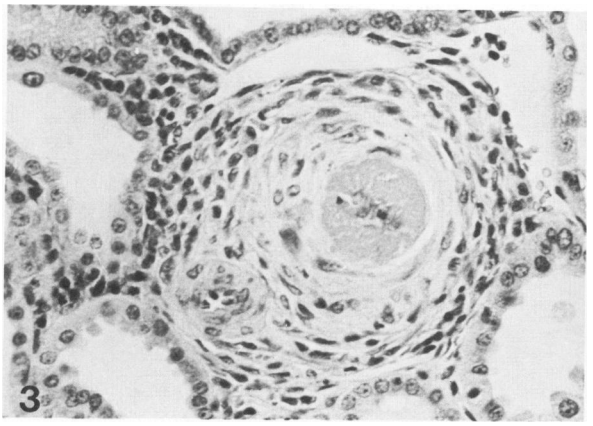


Figure 2— Glomerulus from remnant kidney 3 weeks after ablation. The electron-dense lysosomes in the epithelial cells correspond to the PAS-positive droplets seen by light microscopy. *EPI,* glomerular epithelial cell. *CAP,* capillary lumen. *MES,* mesangial cell. (Uranyl acetate and lead citrate, ×16,000)

of the GECs with PAS-positive cytoplasmic droplets and mesangial expansion remained the principal glomerular lesions in 7 of 11 animals. In 4 animals necrotizing glomerular lesions were seen in 5%, 27%, 31%, and 32% of the glomeruli, respectively. In the area of necrosis there were extensive glomerular fibrin deposits (Figure 5), thrombotic occlusion of capillaries (Figure 6), occlusion of capillaries by swollen endoethelial cells and infiltrating macrophages (Figure 6), and extracapillary extravasation of fibrin and cells (Figure 7). Five animals had segmental glomerular scars (11%, 7%, 16%, 16%, and 3%), and 3 had global



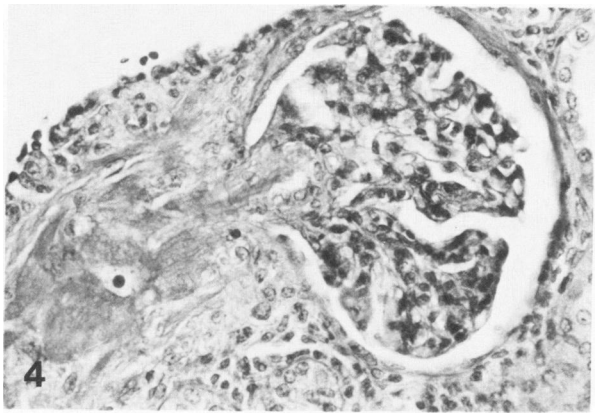


Figure 3— Arteriole from remnant kidney 3 weeks after ablation. The lumen is occluded by a thrombus. There is a swelling of the endothelial cells and proliferation of the underlying myointimal cells. (PAS, ×260) **Figure 4**— Glomerulus from remnant kidney 3 weeks after ablation. The afferent arteriole has undergone fibrinoid necrosis with destruction of the media and aneurysm formation. (PAS, ×260)

Table 2—Semiquantitative Evaluation of Glomerular Damage*

	Overall glomerular damage index	Superficial glomerular damage index	Juxtamedullary glomerular damage index
SHR (6)	0 [0–2]	0 [0–0]	0 [0–0]
Sham control			
3 weeks (5)	4 ± 3 [0–8]	1 ± 3 [1–6]	0 [0–1]
6 weeks (10)	4 ± 8 [0–11]	3 ± 6 [0–15]	2 ± 5 [0–10]
Ablation			
3 weeks (11)	30 ± 18†‡ [1–53]	34 ± 30†‡ [0–88]	32 ± 34†‡ [0–120]
6 weeks (12)	73 ± 62†‡ [0–195]	61 ± 44†‡ [0–157]	70 ± 63†‡ [0–217]

*Results are given as the mean ± SD and range (in brackets). Numbers in parentheses indicate the number of animals.
†The mean is significantly different from the sham operation control value.
‡The mean is significantly different from the SHR value.

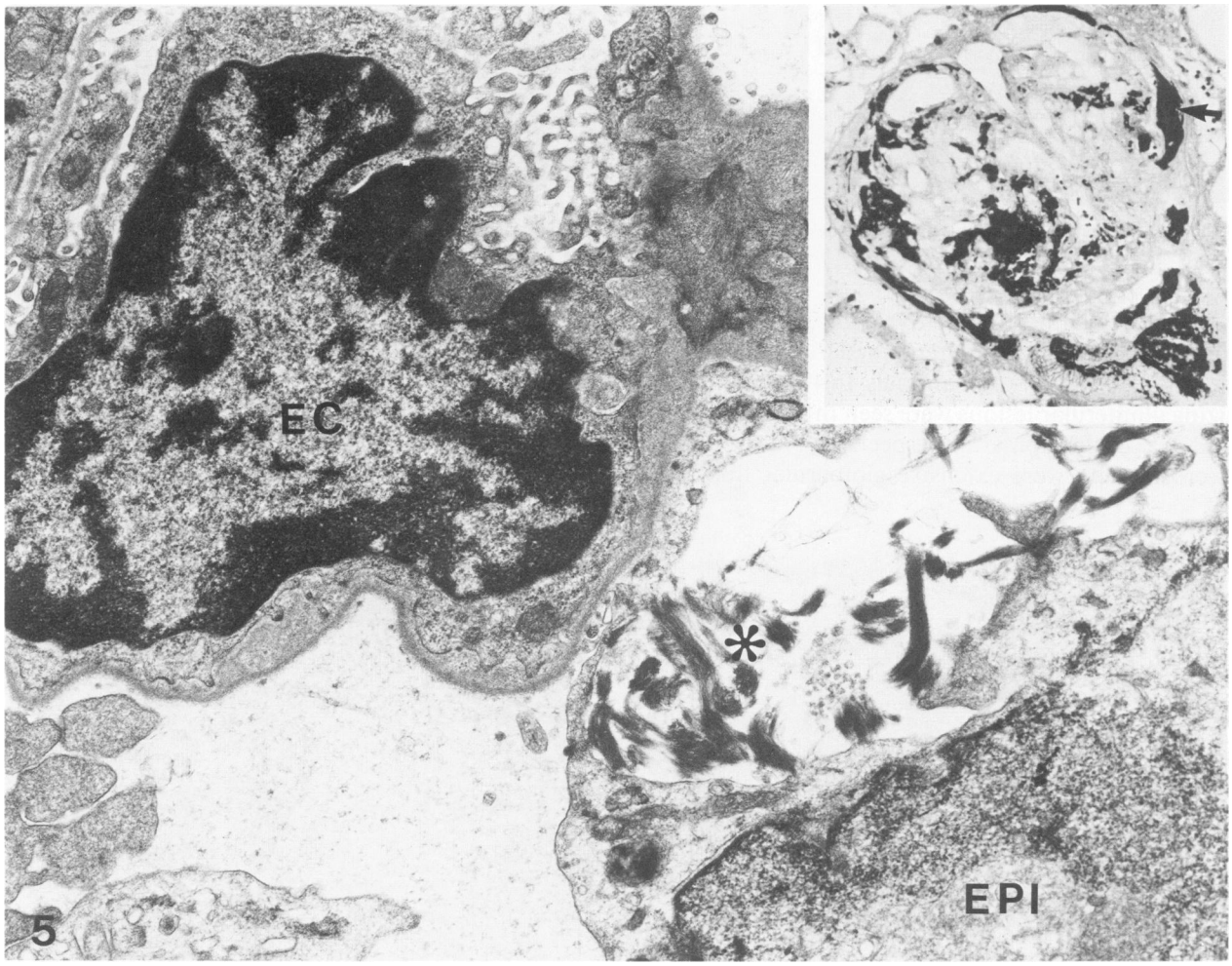


Figure 5—Glomerulus from remnant kidney 6 weeks after ablation. The glomerular capillary is lined by an endothelial cell (EC), but the epithelial cell (*EPI*) has lifted off the basement membrane. Fibrin tactoids (*asterisk*) lie between the epithelial cell and the GBM. (Uranyl acetate and lead citrate, ×16,000 **Inset**—Fibrin is widely deposited within glomerular capillaries, necrotic segments, and free within Bowman's space (*arrows*). (PAH, × 160)

sclerosis of glomeruli (3%, 7% 14%). Four of the 5 cases of segmental sclerosis and 2 of the 3 cases of global sclerosis occurred in the animals with glomerular and vascular necrosis. The 3 animals with widespread glomerular necrosis also had fibrinoid necrosis, thrombosis of arteries (Figure 8), and hyperplastic arteriolitis (onion skin) (Figure 9). Ultrastructural studies of involved glomeruli showed widespread disruption of glomerular capillaries with leukocytic infiltrates and extensive deposits of fibrin. These changes were confined to animals with light-microscopic evidence of severe glomerular damage. The animals with mild glomerular lesions resembled those studied at 3 weeks. There was normal glomerular architecture and only focal foot process fusion, and the GECs remained attached to the basal lamina.

Spontaneously Hypertensive Rats

The glomeruli were normal by light microscopy. The arterioles had subendothelial PAS-positive hyaline deposits, but there was no fibrinoid necrosis, thrombosis, or hyperplastic arteriolitis (onion skin). The arteries were unremarkable.

Controls

The kidneys of the sham operation controls had the same appearance at 3 and 6 weeks. The glomeruli were normal with no evidence of thrombosis, necrosis, hyalinosis or segmental sclerosis. Only a very occasional hyalinized glomerulus was present. The blood vessels were normal, with no medial thickening, hyalinosis, thrombosis, or necrosis.

Protamine Heparin Aggregate Disappearance

Four controls and 4 ablated animals were studied after 3 weeks, and 3 sham and 3 ablated animals were studied after 6 weeks. There was no difference between the disappearance curves of the controls at three (mean one-half disappearance time $- t_{½} = 1.69 \pm 0.22$ hours) and 6 weeks ($t_{½} = 1.57 \pm 0.11$ hours), and they were used to calculate the 95% confi-

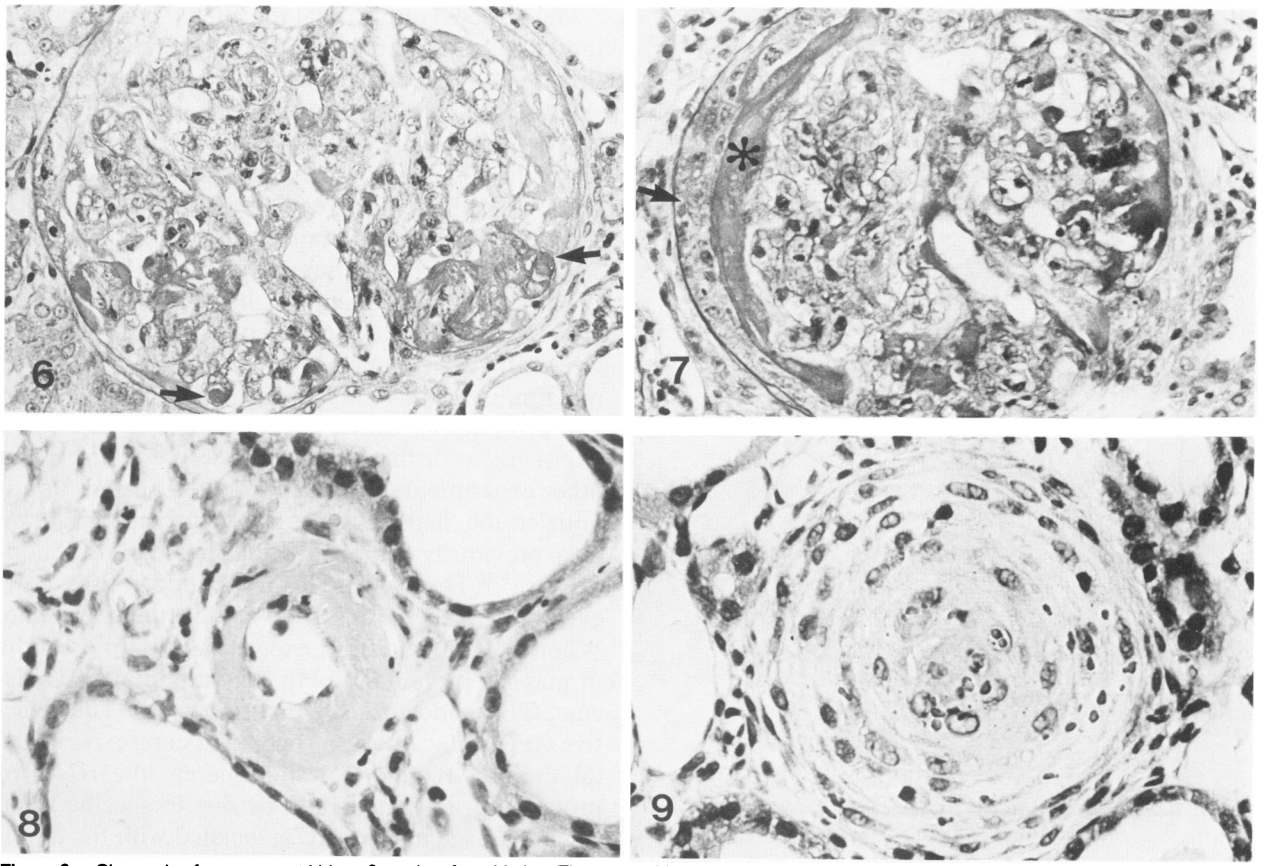


Figure 6 — Glomerulus from remnant kidney 6 weeks after ablation. There are widespread capillary thrombi (*arrows*), karyorrhectic debris, and occlusion of capillaries by swollen endothelial cells and infiltrating macrophages. (PAS ×260) **Figure 7** — Glomerulus from remnant kidney 6 weeks after ablation. In addition to capillary thrombosis and cellular infiltrates, this glomerulus shows a large mass of fibrin in Bowman's space (*asterisk*) and associated cellular proliferation (*arrows*). (PAS, ×260 **Figure 8** — Arteriole from remnant kidney 6 weeks after ablation. The entire wall has undergone fibrinoid necrosis, and the endothelial cells are pyknotic. (H & E, ×260) **Figure 9** — Arteriole from remnant kidney 6 weeks after ablation. There is hyperplastic arteriolitis (onion skin) of an arteriole consisting of a thickening of the vascular wall by proliferation of elongated, concentrically arranged connective tissue cells. The vascular lumen is greatly reduced, and there are red blood cell fragments, nuclear debris, and inflammatory cells scattered throughout the vessel wall. (H & E, 400)

dence limits. The disappearance curve for the ablated animals (Figure 10) at 3 weeks fell within the controls' confidence limits $t_{½} = 1.45 \pm 0.14$ hours). In contrast, GEC endocytosis in the animals with remnant kidneys studied 6 weeks after ablation was impaired ($t_{½} = 2.09 \pm 0.65$ hours). PHA disappeared more slowly from the LRE of the remnant animals than from the sham operation controls, and this decreased rate was more than two standard deviations from the mean disappearance curve of the sham operation controls (Figure 10).

Discussion

The pathogenesis of the segmental glomerular scar that develops in the remnant kidney has become a major subject of investigation because of its putative implications in the pathogenesis of the progression of renal disease in humans with reduced nephron mass. Segmental glomerular sclerosis is a lesion common to diverse forms of progressive renal disease, but the mechanism underlying the formation of the glomerular scar is unknown in most instances. The pathologic features that have been described in the remnant kidney vary, but they include evidence of protein reabsorption by the GECs, acute glomerular injury with fibrinoid necrosis and capillary thrombosis, and glomerular scarring with extravascular protein deposits (hyalinosis). On the basis of morphologic observations, some investigators have suggested that abnormal glomerular permeability,[8] mesangial dysfunction,[14] coagulation abnormalities,[5] and hypertensive injury,[15,16] alone or in concert are the pathogenetic mechanisms that cause the glomerular lesions seen in the remnant kidney. In each case glomerular damage may be directly mediated by the putative mechanism or by the complex factors that compensate for the loss of renal mass in the remnant kidney. In contrast to the mechanisms that are supported by pathologic observations, the hypothesis that hyperfiltration in the remnant glomeruli, by itself, can lead to progressive glomerular sclerosis has been suggested by physiologic studies.[7,17]

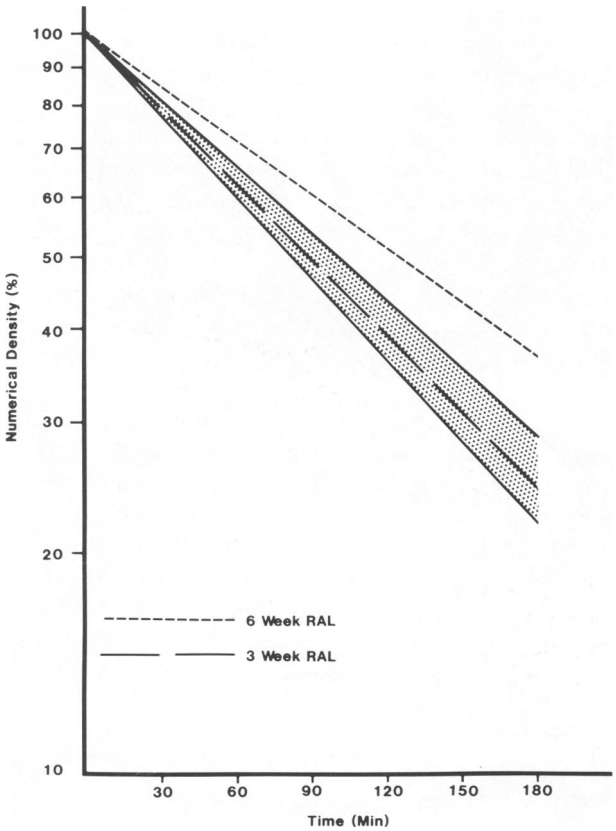


Figure 10 — PHA disappearance curves for rats studied 3 and 6 weeks after renal ablation (*RAL*, remnant kidney model). The *stippled area* represents the 95% confidence limits (2 SD from the mean) for the sham operation controls. After 3 weeks, PHA disappearance is not different from that in the controls, but in rats studied 6 weeks after ablation, the rate of PHA disappearance is significantly less.

Our studies confirm that the altered histologic features of the GEC are a prominent feature of the lesion that develops in the remnant kidney. In order to investigate concomitant functional alterations, we studied the ability of the GECs to ingest foreign aggregates from the glomerular basal lamina. In the normal state, the GECs avidly remove PHAs from the LRE of the glomerular basal lamina by an endocytic process,[18] and the rate of disappearance of PHA from the LRE provides a measure of this function.[10] In rats with a remnant kidney GEC endocytosis is normal 3 weeks after the ablation of approximately 80% of the renal mass. At this time, changes in kidney function and proteinuria, which are seen as early as 1 week after surgery in this model,[4] are well established. In other experimental proteinuric states, such as aminonucleoside nephrosis or Heymann nephritis, we have previously demonstrated decreased GEC endocytosis.[19,20] The decrease in GEC endocytosis is, however, not merely the reflection of the proteinuric state. When administration of exogenous albumin results in massive proteinuria with only minimal GEC disease, GEC endocytosis remains normal.[19] The defective GEC endocytosis that occurs in some experimental models, therefore, is not merely the result of proteinuria, but appears to be due to specific functional damage to the GEC associated with the development of the glomerular lesion. This functional abnormality accompanies morphologic evidence of GEC injury.

The pathologic descriptions of the remnant kidney model suggest that GEC injury may be important in

the evolution of glomerular sclerosis in this model. When we tested this hypothesis after 3 weeks of ablation, the morphologic changes in the GECs were minor and were interpreted as a reflection of increased uptake of filtered plasma proteins, rather than lethal degeneration. The presence of proteinuria in the animals implied that injury to the glomerular capillary wall had already occurred, but GEC endocytosis was normal. Although it is possible that hyperfiltration in the remnant glomeruli leads to GEC dysfunction by a mechanism that is not reflected by the rate of PHA disappearance, normal GEC structure and function, as we are currently able to measure them, militate against this possibility. Later in the course of the remnant kidney model, 6 weeks after ablation, GEC endocytosis was significantly decreased, in comparison with the condition of the control animals. The nature and severity of the concomitant glomerular lesions in the 6-week remnant kidney animals are unlikely to have resulted from a subtle defect in GEC function. However, since we found GEC dysfunction in the context of severe glomerular injury, we are unable to determine whether a causal relationship exists between the functional abnormality and the pathologic lesion, and we cannot exclude a primary role for the GEC in the evolution of glomerular injury and scar formation in the remnant kidney model.

A more likely explanation for the glomerular abnormalities in this model involves the physical effects of barotrauma attendant intraglomerular hypertension on the glomerular capillaries. Shimamura and Morrison first suggested that hyperfiltration is injurious to the remnant glomeruli,[7] and they correlated progressive glomerular sclerosis with an increase in individual nephron glomerular filtration rate that occurs in these animals.[17] Subsequently, micropuncture studies have confirmed directly that the single nephron glomerular filtration rate is increased in the remnant kidney[2,21] as are the intraglomerular hemodynamic determinants of glomerular ultrafiltration, the transcapillary hydraulic pressure and plasma flow rate.[2] A role for hyperfiltration in the pathogenesis of glomerular injury in the remnant kidney model draws further support from several experimental manipulations which modulate hyperfiltration and reduce the incidence of glomerular scarring. However, a straightforward interpretation of the data is made complex because the same manipulations that reduce the glomerular filtration rate and abrogate glomerular injury in the remnant kidney may also reduce systemic blood pressure.[2,4,22-25] The relationship between systemic blood pressure and glomerular capillary pressure is governed by afferent and efferent arteriolar tone, and afferent vasoconstriction protects the glomerular microvasculature from the effects of systemic hypertension. This mechanism is apparently responsible for the absence of acute hypertensive glomerular injury in some experimental models of hypertension and essential hypertension in humans.[25] The absence of glomerular injury in our SHRs demonstrates that systemic hypertension at the level found in the remnant kidney is not sufficient, by itself, to cause acute glomerular necrosis. The transmission of the elevated systemic blood pressure through the dilated afferent arterioles[2] to the glomerulus of the remnant kidney could explain the histopathologic abnormalities seen in this model.[5,15,16] A fundamental physiologic difference between the remnant kidney and models of hypertension with normal renal mass is the presense of renal vasodilatation with reduction of both afferent and efferent arteriolar tone.[2] Dilation of the afferent arteriole implies that in the remnant kidney the glomerular capillaries are more directly exposed to systemic blood pressure and, therefore, are unprotected.

Enthusiasm for the remnant kidney in the rat as a model for various human renal diseases should be tempered by species differences that may exist between this rat model and morbid states in humans.[26] Furthermore, the hemodynamic alterations that follow acute, massive renal ablation may be an appropriate model for the progression of renal disease that follows significant loss of nephron mass, but its relevance to the progression of glomerular disease of insidious onset and slow progression is less clear. Progressive glomerular sclerosis, the hallmark of end-stage chronic glomerulonephritis in humans, has been described in several histologic studies of the remnant kidney. However, they were not a significant feature in our study at 3 weeks. After 6 weeks, segmental glomerular scars were only seen in kidneys with widespread glomerular necrosis and capillary thrombosis. Presumably, these are indicators of active glomerular injury that underlie the process leading to scar formation. A more appropriate clinical correlate for the remnant kidney may be malignant nephrosclerosis. In this condition the preglomerular vasculature is also apparently unable to shield the glomerulus from the destructive effects of systemic hypertension.[27] Although glomerular damage occurs at a lower blood pressure in the remnant kidney, the resulting destructive pathologic lesions have many similarities to those seen in malignant hypertension.

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